## REMARKS

The claims have been amended simply for clarification to note that the neoplastic disease is characterized both by growth at the primary tumor site and metastasis to secondary sites. Support for this language is found, for example, in column 7, lines 9, *et seq.*, and in the discussion throughout the specification. The amendment was not prior made as it was not clear to applicants that there seemed to be some question that the invention subject matter necessarily included study of both primary tumor growth and the metastatic pattern. It is believed that the amendment places the claims in a position for allowance, or certainly in a better position for appeal, and does not raise any new issues. Accordingly, applicants respectfully request entry of the amendment, though made after final.

There is really only one basis for rejection, although tertiary references have been applied to claims 14, 16, 21 and 23 (Giovanella, *et al.*, disclosing models in rats) and claims 18 and 25 (Reddy, *et al.*, disclosing SCID mice). The teachings of these tertiary documents is acknowledged and it is believed that the patentability of the pending claims is not dependent on the use of rats in the model or SCID mice in the model; indeed, it is the purpose of the present reissue application to include these alternatives which were inadvertently not claimed in the issued patent.

Accordingly, this response will treat the rejection over the combination of Kyriazis, *et al.*, in combination with Otto, *et al.*, Wang, *et al.*, and McLemore, *et al.*, as applied to all claims.

The invention, of course, is directed to a model for neoplastic disease progression in humans which involves implanting intact tumor tissue orthotopically into an immunocompromised rodent. It is acknowledged that Kyriazis described an attempt to provide an accurate model of progression using implantation of intact tumor tissue subcutaneously, not

orthotopically, in nude mice. McLemore provides what is intended as a model of disease progression where suspensions of cells are implanted orthotopically in the right lung. It appears that Otto is cited to show that the general technique described by Kyriazis for a number of human tumors is also applicable to renal tumors which are implanted as tumor pieces subcutaneously and Wang appears to be cited for the proposition that the technique of McLemore of orthotopic transplantation of cell suspensions of lung tumors is also applicable to colon tumors.

First, there is no question that, at the time of the original application on which the present application is based (1988), there were a number of studies attempting to establish models based on the approaches described in the cited documents. Kyriazis on page 3995, left-hand column, acknowledges studies employing transplanted human tumors as preserving the morphological, biological and biochemical characteristics of the tumor of origin at least one of which employed intact tumor pieces. McLemore on page 5137, right-hand column, acknowledges six papers which employ orthotopic models where cell suspensions were employed subcutaneously. However, prior to the invention, never the twain shall meet.

Applicants recognize that the model they are claiming in immunocompromised rodents is a combination of selected features of work describing implantation of intact tissue (but done subcutaneously, Kyriazis and Otto) with orthotopic transplantation (but by injection of cells, McLemore and Wang). However, neither camp appears to have recognized the significance of that aspect of the contribution of the other which is employed in the present invention. The Kyriazis paper was published in 1981, and the McLemore paper was published in 1987. On this basis alone it is seen that after six years, the art had not seen fit to transplant intact tissues orthotopically.

The Office objects to applicants' previous responses said to criticize the documents individually; applicants point out these deficiencies in the cited documents not because applicants have misinterpreted the rejections as rejections for anticipation or because applicants fail to recognize that it is the combined teachings of the references that are important. These deficiencies are pointed out to show that the results obtained with the claimed models are unexpected and surprising in view of the notable lack of success of prior art models. This will further be addressed below; the argument begins with a lack of motivation to combine the documents cited.

The Office asserts that the motivation to combine Wang and McLemore with Kyriazis lies in the asserted disclosure by Wang and McLemore that orthotopic implantation is superior to other models. First, it is not at all clear that Wang makes this assertion. Indeed, the last sentence of Wang states that the gut versus SC implanted tumors showed a slower growth rate at given time intervals. While Wang states that colonic tumors invaded various subregions of the colonic wall and mimic the original pattern characteristic for patient tumors, nothing is said about the pattern exhibited by SC implanted cell suspensions.

McLemore indeed postulates that the orthotopic model employed (cell suspensions) is superior to subcutaneous models. A fair reading of the paper, however, would lead one to conclude that in the view of McLemore, the model actually proposed is just fine. As stated by McLemore in the closing comments, "This intrapulmonary model has several advantages over other currently available models and should be of particular value for future studies of lung cancer biology and treatment." Indeed, McLemore finds nothing wrong with the model proposed. Further, in comparing the results obtained orthotopically with a subcutaneous model, success of the orthotopic model was not evaluated with respect to faithfulness to disease progression patterns, but rather with respect to effectiveness in propagation of human lung tumor

cells (page 5136-5137, bridging paragraph). In short, the reader of McLemore has no motivation to combine McLemore with anything else at all based on McLemore's touting of his own orthotopic model, not orthotopic models in general.

Perhaps the skilled reader of McLemore might be motivated to improve on McLemore's model by the fairly dismal results obtained in mimicking human disease when examined objectively. On page 5136, right-hand column, it is noted that 91% of the tumors in McLemore's model were localized to the right lung, whereas in only 1% of the cases did the tumors metastasize to the left lung and in only 6% of the cases did the tumors metastasize to the paratracheal area. These sites of metastasis are very common in human lung tumors; indeed, were this not the case, the death rate from lung cancer would be much lower since all that would need to be done is to remove the affected lung. The remaining lung would be sufficient to sustain at least some quality of life.

But even assuming that the skilled reader would note that the model proposed by McLemore is inadequate (it is pretty difficult to evaluate the model described by Wang as either good or bad), no reason is given as to why the reader would turn to Kyriazis to remedy this. And there is no reason. Like McLemore, Kyriazis is entirely content with the results obtained, indicating that Kyriazis is puzzled by reports by leading investigators on the absence of metastases (page 3995, left-hand column). Kyriazis is unable to show typical patterns of metastasis as well.

The Office notes that Kyriazis' "primary interest is in lymph nodes and lungs" and that therefore, it is impossible to determine whether other tissues exhibited metastasis or not. However, this is not the case. At page 3995, right-hand column, it is noted that "tumors, regional and distant lymph nodes and representative sections *from various organs* were fixed in 10% buffered formalin solution. Removal and processing of lungs was done as described previously."

Thus, it appears that lymph nodes and lungs were removed, but various organs, in addition were fixed in 10% formalin solution, and thus examined. Had metastases appears in these organs, they would have been reported. Apparently some were found in the diaphragm as the Office notes.

As noted in Dr. Hoffman's previous declaration, the liver is (and was known in 1988) to be the primary site of metastases from colon. Apparently, none were found in the liver by Kyriazis. The metastatic patterns observed by Kyriazis were on their face deficient as admitted by Kyriazis himself "absence of metastases should be viewed within the context of the tumor host relationship and tumor biology rather than as evidence of benign tumor behavior." This is a cautionary statement to explain the obvious failure admitted by Kyriazis to observe metastases expected. Kyriazis viewed observation of metastases in lungs as:

> [A]n indication of the positive metastatic potential of the transplanted tumors regardless of the *absence of recognizable large tumor formations*. Failure to detect the latter may be related to various host factors, *e.g.*, mouse strain, health status of animals and site of transplantation, tumor size and growth rate and the biological characteristics of the original neoplastic growth from which the transplanted tumor originated. Furthermore, since metastases are not synchronous those taking place late in the life of the animal may not have the time required to reach the stage of detectability, being only microscopically seen as small aggregates or neoplastic cells within lymphatic channels and pulmonary vessels. (Emphasis added.)

In other words, Kyriazis recognizes that metastases that would have occurred in the human patients simply were not observed in the mouse. This is despite the fact that the tumors were allowed to grow to considerable size before the mice were sacrificed (see page 3995). (The calculated diameter of these tumors is on the order of 1.6 cm. using the formula provided.)

Thus, even if a reader of McLemore were persuaded by the inadequacies of the McLemore model (as evidenced by the unexpectedly low rate of metastasis) as a reason to

improve the model, the skilled artisan would hardly be led to Kyriazis whose results are even worse.

This brings the discussion to the issue of unexpected results. As stated above, there is no motivation whatsoever to combine the teachings of Kyriazis with those of McLemore. Both orthotopic cell suspension models and subcutaneous intact tumor models had been in coexistence for at least seven years prior to the date of the present invention, and only the applicants sought to combine these teachings. Their combination, as unsuggested as it was by the art, even if obvious to try, provided unexpectedly excellent results. These results have been set forth in the declaration of Dr. Robert Hoffman filed with the previous response indicating the great success of the claimed model. In view of the lack of success of both precursor models (only one element of each being used in the claimed model system), it could not have been predicted that the combination of orthotopic implantation with the use of intact tumor tissue would provide the successful results exhibiting faithful replication of the ability of tumors to metastasize in human patients as exhibited by the multiple publications from the laboratory employing this method, enclosed with the previous response.

Accordingly, it is believed that the rejection of the pending claims as obvious over the art is properly withdrawn.

## CONCLUSION

The claims have been amended to clarify that metastasis is an integral part of the progression of neoplastic disease measured by the models of the claimed invention. Entry of the amendment, though made after final, is respectfully requested in view of its clarifying nature. Applicants acknowledge that the invention is a combination of a selected element from each of two commonly used models for neoplastic disease; for the reasons stated above, combination of these two features is not suggested by the art, but only by the invention itself and is thus not

*prima facie* obvious. The Office has failed to show any motivation for combining these particular elements. Further, the results obtained with the claimed model are unexpectedly faithful to the human course of disease and have enjoyed considerable commercial success. Thus, it is believed that the rejection of the pending claims should be withdrawn and these claims be passed to issue forthwith.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 312762001530.

Respectfully submitted,

Dated: November ___, 2003 By: _____

Kate H. Murashige
Registration No. 29,959

Morrison & Foerster LLP
3811 Valley Centre Drive, Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5112
Facsimile: (858) 720-5125